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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,078	03/15/2004	Krzysztof Palczewski	029060-000200US	9475

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
10/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,078	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/23/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20,35-37 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20,35-37 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/2009, 7/28/2009, 1/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Status of Application

1. The response filed July 27, 2009 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claims 16-20,35-37 have been amended.

   b. Claim 21, 38-43, 45, 47-48 has been cancelled.

   c. Claim 49-51 has been added.

2. Claims 16-20, 35-37, 49-51 are pending in the case.

3. Claims 16-20, 35-37, 49-51 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

Information Disclosure Statement

6. The information disclosure statement filed 9/23/2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because there is no copy of any of the references in the IDS. All 105 references in the filed were reviewed but there is no copy present. Applicant is welcome to identify when they were submitted if this is in error. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes

of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

7. Claims 19 and 35 are objected to because of the following informalities: The claims have been amended but have claim identifiers that cite them to be "Original" and "Previously presented" which are the incorrect claim identifier. Appropriate correction is required.

Election/Restrictions

8. Applicant had previously elected the species 11 cis-7-ring retinal for examination on February 8, 2008. Claims 47-48 where later added and withdrawn due to the election of the 11-cis-7-ring retinal. Applicant asserts that claim 47 with withdrawn in error as it contained the 20carbon backbone of the 11-cis retinal. The argument is moot as the claim is cancelled but for clarification this is not persuasive as a 11-cis retinal derivative as written did not have the 7-ring formation structurally and forms the locked position as presented in the elected species whereby withdrawal is proper.

Currently, the new claims presented at RCE do not read on the elected species of 11 cis-7-ring retinal. Whereby it is the discretion of the Examiner to choose the new species for examination if needed, or send a new election of species requirement. While Applicant a shift of species with an election of the compound of claim 20 and oral administration, there currently will be no election of species requirement sent, the

preemptive election while appreciated is currently moot, claim 20 is subject to the 112 rejections below, and if an election is needed in the future, a election will be available for Applicant to choose their desired species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 16-20, 35-37, 49-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are directed to a 9-cis retinal derivative, wherein said derivative is a modification of the polyene chain with a retention of the polyene chain length and retention of the 9-cis bond. The area of support as directed by Applicant is paragraph 31 and 37 of the U.S. Pat. Publication of the instant application. The paragraph of the publication does not support the amendment to the claims. The paragraphs directed by Applicant are directed to two different formulas (formula II and formula VII) which have different recitations for the formulas. The paragraphs are also supportive for 9-cis retinal derivatives with modified polyene chain length which is to formula II (paragraph 31) or a modified polyene chains is the modification of cis and trans bonding (formula VII) separately, but not together. It does not support for the combination recitation of a 9-cis retinal derivative with is a

modification of the polyene chain with a retention of the polyene chain length and retention of the 9-cis bond. It is also noted that it appears that recitations of formula III (paragraph 33-34) are utilized for the claims which are for substitutions along the chain but not within the chain wherein the claim is unclear if modification of the chain includes substitution of the chain rather than along the chain as indicated by formula III which is still not to be combined with the other formulas as written in the specification. It also appears that components of formula III are combined with components from Formula VII to create the structure of claim 20 which is new matter as the two different formulas have different recitations for each formula and do not support select combination from each. It may be helpful for there to be a specific formula directly supported by the specification to be recited to limit the 112 issues. This also applies to the structure of claim 19 as there is no compound with those recitations and the claims is also unclear on the metes and bounds as addressed by the 112 2nd rejections below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 16-20, 35-37, 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are unclear as to the issue of derivative. The term "derivative" is indefinite as it unclear is encompassed by the term and given the form any number of compounds given an infinite number of chemical reactions, the compounds and be anything and thereby it is unclear what is envisioned

for the invention. It does not allow one of skill in the art to know the metes and bounds of the invention.

It is also unclear what constitutes a modification of the polyene chain, whether it is substitution off the chain or substitution of elements of the chain. It is unclear as written if the ring and the aldehyde of the retinal is subject to modification along with the chain or if the derivation is only in the polymeric chain. It is also unclear if the retinal upon derivation remains a retinal which by definition of a retinal would require an aldehyde group (retinal verses retinol) which if subject to derivation could not be present and would no longer be a retinal which is reflected in claim 19 which can have R9 as alkyls which converts the compound to a ketone and would not remain a retinal (an aldehyde). It is also unclear if the structure is the resulting derivative or a base of derivation. It does not allow one of skill in the art to ascertain the metes and bounds. For purposes of prosecution for claims 16-19, 35-37, 49-51, any retinal with a 9-cis bond applies. Claim 20 is subject to the rejection below.

11. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim as presented is pixilated and the Examiner is unable to discern the subscripts for the R groups in the claim even with enhancement. It is unclear if the R designations are R1 or R2 or R3 for the first recitation, if it is R3, R6, R8,or R9 for the second recitation, and if R8 or R9 for the third recitation wherein these are just the best guesses. The claim cannot be further treated on the merits. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 16-19, 35-37, 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa).

Chapple et al. teaches that retinitis pigmentosa is he most common cause of inherited blindness. The most frequent mutation and misfolding mutation in rhodopsin is the proline to histidine change at residue 23 (P23H). Chapple et al. teaches that 9-cis retinal can improve folding of the mutant rhodopsin in T17M mutant opsin and in P23H mutant opsin allowing improved movement of opsin to reach the plasma membrane, whereby the retinoid can be used as a 'chemical' chaperone to stabilize the folding of the mutant opsins shifting the equilibrium toward functional proteins. Chapple teaches that is known in the art that Vitamin A has some therapeutic value in retinitis pigmentosa. Chapple also teaches that while the trial was not focused on patient with the these misfolded mutations, if they had, the clinical outcomes may have been even better and that further investigation of these methods may lead to therapies for the misfolded protein disease and other conditions.

Chapple does not expressly teach an example with administration to a human. Chapple does however, teach the benefit of 9-cis retinal in improving the P23H mutant protein to forming functional opsin and teaches that had the trial been with patients with the misfolded mutants, the outcome could be even better, wherein Chapple already has described utilizing the 9-cis retinal on human patients with the misfolded P23H opsin. It would have then been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the 9-cis retinal for a patient with P23H retinitis pigmentosa as described by Chapple, and produce the instant invention. It would have been obvious to approach this next step and one of skill in the art would be motivated to do so, as it is already described by Chapple and pursue this next phase as typical in the art to move from animal/lab models to human subjects with the condition as the progression to developing an effective, safe, and therapeutic treatment for any condition. It is also obvious and known by one of skill in the art that the active (9-cis-retinal) would have to be in a pharmaceutically acceptable carrier as an active cannot be given without a carrier which is the motivation if one wants to administer any active. It is noted that when the active is administered as claimed, the mechanism of action is intrinsic to the composition and mode of administration.

13. Claim 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Lang (Ocular drug delivery conventional ocular formulations) and Geroski et al. (Drug Delivery for Posterior Segment Eye Disease).

The teachings of Chapple et al. are addressed above.

Chapple does not expressly teach eye drops, intraocular injection, and periocular injection.

Lang teaches that there are commonly known dosage forms for ocular drug delivery including solutions (eye drops) , suspensions (eye drops), and injectables (Abstract, Table 1).

Geroski et al. is presented merely to demonstrate that there are known types of ophthalmic injections to one of skill in the art for drug delivery including intraocular and periocular (Page 961, second column).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize known modes of ophthalmic drug delivery including drops and injections such as periocular and intraocular, as suggested by Lang and Geroski, and produce the instant invention. It would be obvious to utilize any of the known and conventional modes of administration forms to deliver any active for an eye condition including drops and injections depending on the therapeutic profile desired as these are well known conventional modalities in the art.

One of ordinary skill in the art would have been motivated to do this because it is desirable to utilize known modes of administration and have different forms of administration to affect the condition to be treated in the most effective manner and therapeutic profile desired for the patient.

Response to Arguments

Applicant's arguments with respect to the previous claim rejections have been considered but are moot in view of the new amendments to the claims.

Conclusion

14. Claims 16-20, 35-37, 49-51 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612